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Applicant: Arthur Palmer)
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I hereby certify that this paper is being transmitted via facsimile to: Assistant Commissioner for Patents, Washington, D.C. 20231, on this date.

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Assistant Commissioner for Patents
Washington, D.C. 20231

AMENDMENT TRANSMITTAL

Sir:

Transmitted herewith is a communication regarding the above-identified application.

Fee Calculation For Claims As Amended

	As Amended		Previously Paid For		Present Extra		Rate		Additional Fee
Total Claims	22	-	34	=	0	x	$18.00	=	$ 0
Independent Claims	9	-	11	=	0	x	$84.00	=	$ 0
Fee for Multiple Dependent Claims							$280.00	=	$
					Total Additional Fee				$ 0

(X) Applicant is an independent inventor and Small Entity, reducing Filing Fee by half to: $ 0

(X) Amendment B with Version with Markings to Show Changes Made, and attached Journal Articles and Patent.

(X) The Commissioner is hereby authorized to charge any additional fees which may be required to this application under 37 C.F.R. §§1.16-1.17, or credit any overpayment, to Deposit Account No. 07-2069. A duplicate copy of this sheet is enclosed.

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Handbook of Dialysis

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Little, Brown and Company
Boston/Toronto

Serum parathyroid hormone and aluminum concentrations should be measured at 6-month intervals, particularly in patients ingesting aluminum-containing phosphate binders.

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Anticoagulation

Gerard A. Zasuwa, Francis Dumler, John T. Daugirdas, and Nathan W. Levin

Heparin is used routinely to anticoagulate the blood during hemodialysis. In high-risk patients hemodialysis can be performed using a reduced dose of heparin ("light heparin") or without heparin ("heparin-free" or "regional citrate" methods).

I. **Monitoring coagulation during dialysis**

A. **Clotting time tests.** Three tests are commonly used.

1. **Whole blood partial thromboplastin time (WBPTT).** The WBPTT test accelerates the clotting process by addition of 0.2 ml of actin FS reagent (Thromboplax) to 0.4 ml of blood. The mixture is set in a heating block at 37°C for 30 seconds and then tilted every 5 seconds until a clot forms. The prolongation of the WBPTT is linearly related to the blood heparin concentration (in the range applicable to dialysis).
2. **Activated clotting time (ACT).** The ACT test is similar to the WBPTT but uses siliceous earth to accelerate the clotting process. The ACT is less reproducible than the WBPTT, especially at low blood heparin levels. Devices that automatically tilt the tube and detect clot formation facilitate standardization and reproducibility of both the WBPTT and the ACT.
3. **Lee-White clotting time (LWCT).** The Lee-White test is performed by adding 0.4 ml blood to a glass tube and inverting the tube every 30 seconds until the blood clots. Usually, the blood is kept at room temperature. Disadvantages of the LWCT test include the long period of time required before clotting occurs and the relatively poor standardization and reproducibility of the test. The LWCT is the least desirable method of monitoring clotting during hemodialysis.

B. **Where to sample the blood.** Blood for clotting studies should be drawn from the arterial line, proximal to any heparin infusion site, to reflect the clotting status of the patient, not that of the extracorporeal circuit.

C. **Variability in clotting times among different dialysis centers.** A number of target clotting times during dialysis are listed in Table 7-1. The values given may not be appropriate for all dialysis centers because baseline clotting times (off heparin) will vary among different units, depending on techniques and reagents used. Each dialysis center should establish its own range of normal values. If the range of normal is different from that listed in Table 7-1, the target clotting times may also need to be adjusted.

II. **Heparin prescriptions.** There are two heparin regimens in common use: a routine regimen and a tight regimen. The latter is used for patients at risk for bleeding. A third method, designed for patients with a very high bleeding risk, was called the "regional" heparin technique and involved infusion

of protamine into the venous line to neutralize any administered heparin. Regional heparinization has now been largely replaced by the tight-heparin, heparin-free, and regional citrate methods mentioned above and discussed later in this chapter.

A. Routine heparin

1. Target clotting times. For patients who are at low bleeding risk and who do not have pericarditis, heparin can usually be given rather liberally during dialysis without fear of precipitating a bleeding episode. The effect of two routine heparin regimens on clotting time is shown in Figure 7-1. The goal is to maintain the WBPTT or ACT at the baseline value plus 80% during most of the dialysis session. However, at the end of the session the clotting time should be shorter (baseline plus 40% for the WBPTT or ACT) to minimize the risk of bleeding from the access site after withdrawal of the access needles.

In patients with a baseline WBPTT or ACT that is prolonged out of the normal range, further prolongation of the clotting time to baseline plus 80% during dialysis may be associated with bleeding and is not necessary. For this reason the target WBPTT or ACT during dialysis should not exceed 180% of the average baseline value of the patients in the dialysis center.

The target clotting times using the Lee-White test are also listed in Table 7-1. With the LWCT, in contrast to the WBPTT or ACT, the target clotting

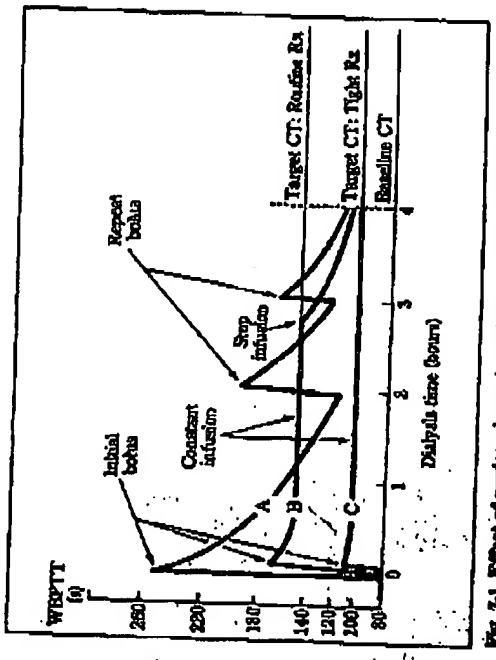

Fig. 7-1. Effect of various heparin regimens on the clotting time as reflected by the whole blood partial thromboplastin time (WBPTT). CT = clotting time using the WBPTT test. A = routine regimen, repeated bolus method; B = routine regimen, constant infusion method; C = tight regimen, constant infusion method.

Table 7-1. Target clotting times during dialysis

			Routine heparin		Tight heparin	
			Desired range		Desired range	
Test	Reagent	Baseline value	During dialysis	At end of dialysis	During dialysis	At end of dialysis
WBPTT[a]	Actin FS	60–85 s	+80%	+40%	+40%	+40%
ACT[a]	Siliceous earth	120–150 s	(120–140) +80%	(85–105) +40%	(85–105) +40%	(85–105) +40%
LWCT[a]	None	4–8 min	(200–250) 20–30	(170–190) 9–16	(170–190) 9–16	(170–190) 9–16

WBPTT = whole blood partial thromboplastin time; ACT = activated clotting time; LWCT = Lee-White clotting time.
[a] There are various methods of performing the ACT, and the baseline value with some methods is much lower, i.e., 80–120 seconds.
[b] Baseline values of the LWCT vary greatly depending on how the test is performed.

times during dialysis are considerably greater than baseline plus 80%, and the target LWCTs at the end of the session are greater than baseline plus 40%.

2. **Routine heparin prescriptions.** There are two techniques of administering routine heparin. In one method a heparin bolus is followed by a constant heparin infusion. In the second, a heparin bolus is followed by repeated bolus doses as necessary. For purposes of discussion we present a typical prescription in each category.

Rx: Routine heparin, constant infusion method

1. Administer the initial bolus dose, e.g., 2000 units.
2. Start dialysis and also start heparin infusion into the arterial blood line, e.g., at a rate of 1200 units/hour.
3. Monitor clotting time (WBPTT, ACT, or LWCT) every hour. Adjust the heparin infusion rate to keep:
   a. The WBPTT or ACT at baseline plus 80%, *but* not more than 160% of the average baseline value for patients in the dialysis center, *or*
   b. The LWCT at 20–30 minutes.
4. Stop the heparin infusion 1 hour before the end of dialysis.

Rx: Routine heparin, repeated bolus method

1. Administer the initial bolus dose; e.g., 4000 units.
2. Monitor clotting times every hour:
   If a. WBPTT or ACT is less than baseline plus 50% or
   b. LWCT is less than 20 minutes,
   Then give an additional 1000–2000-unit bolus dose and repeat the clotting time in 30 minutes. (Normally, one or two additional doses of heparin are given during the dialysis session.)

With the constant infusion method the initial bolus dose of heparin is lower (2000 units) than with the repeated bolus method (4000 units) because with constant heparin infusion the initial bolus dose is required to prolong the ACT or WBPTT to only baseline plus 80% (see curve B in Fig. 7-1). On the other hand, with the repeated bolus technique the initial bolus dose is designed to prolong the clotting time initially to well above the "baseline plus 80%" value (see curve A in Fig. 7-1).

a. **Indications for altering the suggested initial bolus heparin dose**
   (1) **Increasing the dose.** An initial bolus dose of 2000 units of heparin (constant infusion method) will not increase the WBPTT to baseline plus 80% in all patients; the dose required to achieve a baseline plus 80% prolongation can range from 500 to 4000 units, depending on the sensitivity to heparin of the individual patient and on the actual potency of the heparin preparation being used. The WBPTT or ACT can be checked 3 minutes after giving the initial 2000 units; if the prolongation of the clotting time is insufficient, a second bolus dose can be promptly administered. The prolongation of WBPTT or ACT will be directly proportional to the amount of heparin given, e.g., if the initial heparin bolus has prolonged the WBPTT by 40 seconds, then a supplementary dose of half the initial amount will increase the WBPTT by an additional 20 seconds.

   (2) **Reducing the dose**
      (a) **Prolongation of baseline bleeding and clotting time.** With both the constant infusion and repeated bolus techniques, the initial bolus dose of heparin should be reduced in extremely uremic patients in whom uremia-induced platelet dysfunction may have prolonged the bleeding time, and in all patients in whom the baseline clotting time (off heparin) is prolonged.
      (b) **Repeated bolus method, short-session dialysis.** When using the repeated bolus technique, the initial suggested heparin dose of 4000 units may need to be reduced in patients who are to be dialyzed for only a short period of time (e.g., 2 hours). If the bolus dose anticoagulates the patient excessively, then the clotting time may still be markedly prolonged at the end of dialysis, resulting in bleeding from the access site when the needles are removed.
   (3) **Effect of body weight on the size of the heparin dose.** In adult patients weighing between 50 and 90 kg, the sensitivity to heparin does not appear to be related to body weight. Within this population there is no reason to modify the suggested heparin doses because of body weight.

b. **Determination and adjustment of the heparin infusion rate.** The "average" heparin infusion rate required to maintain the WBPTT or ACT at baseline plus 80% is 1200 units/hour, but the infusion rate can range from 500–3000 units/hour. The required infusion rate is based on both the patient sensitivity to heparin and the heparin half-life. Once a steady state has been reached, the infusion rate is directly proportional to the prolongation of the WBPTT or ACT. Hence, if an infusion rate of 1200 units/hour is causing a 60-second prolongation of the WBPTT, then an infusion rate of 1800 units/hour will effect an overall prolongation of 90 seconds, and a rate of 600 units/hour will cause an overall prolongation of 30 seconds.
   (1) **Importance of being at steady state.** It is difficult to adjust the heparin infusion rate if the patient's clotting times are changing; i.e., if

the patient has not reached steady state. This is especially a problem when the initial bolus dose of heparin was incorrect and resulted in an initial WBPTT or ACT value that was much longer or shorter than the baseline plus 80% value.

c. **When to terminate the heparin infusion.** The heparin half-life in dialysis patients averages 60 minutes but ranges from 30 minutes to 2 hours. Because the prolongation in WBPTT is directly proportional to the plasma heparin level, if one knows the current prolongation of WBPTT, then one can predict the prolongation in WBPTT at any future time (assuming no further heparin is administered) based on the heparin half-life in that particular patient. For example, assume that in a given patient the heparin half-life is 1 hour. If the current prolongation in WBPTT is 60 seconds (e.g., current WBPTT 135 seconds, baseline 75 seconds), in 1 hour the plasma heparin level will have decreased by 50%, at which time the prolongation in WBPTT will be only 30 seconds. Similarly, after an additional hour, the prolongation in WBPTT will be only 15 seconds.

The exact calculation of the time at which to stop a heparin infusion based on the heparin half-life can be found in the article by Gotch and Keen. For a patient with an average heparin half-life of 1 hour, if the heparin infusion during dialysis is prolonging the WBPTT or ACT to the required baseline-plus-80% value, stopping heparin administration approximately 1 hour prior to the end of dialysis will result in the desired WBPTT or ACT value of baseline plus 40% at the termination of the session.

B. Tight heparin

1. **General comments.** Tight heparinization schemes are recommended for patients who are at slight to moderate risk for bleeding (Table 7-2). When using the WBPTT or ACT to monitor therapy, the target clotting time (see Table 7-1 and curve C in Fig. 7-1) is equal to the baseline value plus 40%. Target clotting times using the Lee-White method are given in Table 7-1. Again, in some patients the baseline WBPTT or ACT values will be prolonged beyond the normal range, and the target WBPTT or ACT value should not be more than 140% of the average baseline value for patients in the dialysis unit.

   In the tight heparin technique, when it is desired to estimate the patient sensitivity to heparin (see below), the initial heparin dose is best administered to the patient via the venous access tubing and flushed in with saline (rather than being infused into the arterial blood line).

2. **The tight heparin prescription.** A bolus dose followed by a constant infusion of heparin is the best technique for administering a tight heparin prescription, because constant infusion avoids the rising and falling clotting times that are inevitable with repeated bolus therapy. A repeated bolus method (1000 units loading dose followed by bolus doses of 500 units as needed to keep the WBPTT or ACT above baseline plus 25%) can be used when machines with a heparin pump are not available. A typical tight heparin prescription is as follows:

Table 7-2. Anticoagulation strategy

Moderate bleeding risk (tight heparin)	High bleeding risk (heparin-free or regional citrate)
Pericarditis	Pericarditis
Recent surgery (low bleeding risk)	Recent surgery with bleeding complications
	Recent surgery after which bleeding would be very dangerous
	Vascular and cardiac surgery
	Eye surgery (retinal and cataract)
	Renal transplant
	Brain surgery
	Coagulopathy
	Thrombocytopenia
	Intracerebral hemorrhage
	Any active bleeding

Rx: Tight heparin, constant infusion method

1. Obtain baseline clotting time (WBPTT or ACT).
2. Initial bolus dose = 750 units.
3. Recheck WBPTT or ACT after 3 minutes.
4. Administer a supplemental bolus dose if needed to prolong WBPTT or ACT to a value of baseline plus 40%.
5. Start dialysis and heparin infusion at a rate of 600 units/hour.
6. Monitor clotting times every 30 minutes.
7. Adjust the heparin infusion rate to keep the WBPTT or ACT at baseline plus 40% (but not longer than 140% of the average baseline value of patients in the unit).
8. Continue the heparin infusion until the end of the dialysis session.

a. **Determination of the optimum initial bolus dose.** Depending on the heparin sensitivity of the patient and the actual potency of the heparin preparation used, the initial dose required to achieve a 40% prolongation of the baseline WBPTT or ACT value can range from 300 to 2000 units. For this reason, when administering the "usual" 750-unit dose to an unknown patient, it is wise to wait and

recheck the WBPTT or ACT 3 minutes after having administered the bolus dose. Great care must be exercised when drawing the blood for these clotting studies, to avoid contamination of the sample with residual heparin or saline in the vascular access tubing. If the clotting time is insufficiently prolonged by the initial 750-unit bolus dose, then a supplementary bolus dose should be administered. For example, if an initial bolus dose of 750 units prolonged the WBPTT by 20 seconds, then an additional 375 units will prolong the WBPTT by 10 more seconds.

b. **Adjusting the heparin infusion rate.** For a tight heparin prescription the average infusion rate required to maintain the WBPTT or ACT at baseline plus 40% will be approximately 600 units/hour but can range from 200 to 2000 units/hour. If the initial bolus dose of 750 units resulted in a prolongation of the WBPTT that was much smaller or larger than expected, the first estimate for the proper infusion rate (600 units/hour) should be revised accordingly.

EXAMPLE

If the initial dose of 750 units prolonged the WBPTT by only 20 seconds instead of the required 30 seconds, the correct move is to give an additional 400-unit bolus, and then start the heparin infusion at a rate of 1200 units/hour instead of the usual 600 units/hour. If, on the other hand, the initial 750 units prolonged the WBPTT by 60 seconds instead of the required 30 seconds, one should start dialysis and not start the heparin infusion, checking the clotting times periodically. Once the WBPTT has fallen to +30 seconds (baseline plus 40%), the infusion should be started, but at a reduced rate of 300 units/hour.

Whether or not the heparin sensitivity is close to the expected value, the initial estimated infusion rates may need to be increased or decreased due to different heparin half-lives in different patients. The adjustment should be made based on close monitoring of the clotting time. For methods to directly calculate the heparin infusion rate and half-life, see Gotch and Keen.

C. **Heparin-free dialysis**

1. **General comments.** The success of heparin-free dialysis is rendering tight heparin regimens obsolete. The indications for heparin-free dialysis are listed in Table 7-2. Heparin-free dialysis is the method of choice in patients who are actively bleeding, who are at high risk of bleeding, or in whom the use of heparin is contraindicated (e.g., patients with heparin-induced thrombocytopenia).
2. **The heparin-free prescription.** There are a variety of techniques, but all are quite similar to the one given below:

Rx: Heparin-free dialysis

1. *Heparin rinse.* Rinse extracorporeal circuit with saline containing 3000 units heparin/liter. To prevent heparin administration to the patient, flush the heparin-containing priming fluid to drain by filling the extracorporeal circuit with either the patient's blood or with unheparinized saline at the outset of dialysis.
2. *High blood flow rate.* Set blood flow rate as high as possible, at least 250–300 ml/minute if tolerated. If a blood flow rate of at least 250 ml/minute is contraindicated due to the risk of disequilibrium (e.g., small patient, very high predialysis plasma urea nitrogen level), consider using regional citrate anticoagulation instead.
3. *Periodic saline rinse.* Every 15–30 minutes, rinse the dialyzer rapidly with 100–200 ml of saline while occluding the blood inlet line. Adjust the transmembrane pressure (TMP) to remove this extra rinsing fluid from the circulation. Use of an ultrafiltration controller is required. The purpose of the periodic rinsing is to allow inspection of a hollow-fiber dialyzer for evidence of clotting. Also, the periodic saline rinsing may of itself reduce the propensity for dialyzer clotting.

3. **Different membranes and parallel-plate versus hollow-fiber dialyzers.** We prefer to use polyacrylonitrile parallel-plate dialyzers to perform heparin-free dialysis, although others have been successful using cellulose acetate and cuprammonium cellulose hollow-fiber dialyzers. There is no solid evidence to suggest that parallel-plate dialyzers are better than hollow-fiber dialyzers for heparin-free dialysis or that any one type of membrane material is superior.
4. **Expected incidence of clotting.** Using the above method of heparin-free dialysis, complete clotting of the dialyzer will occur in approximately 5% of cases, an acceptable risk that more than balances the danger of bleeding associated with heparin administration to high-risk patients.
5. **Blood or lipid emulsion administration** during heparin-free dialysis may increase the risk of clotting.

D. **Regional citrate anticoagulation.** An alternative to heparin-free dialysis is to anticoagulate the blood in the extracorporeal circuit by lowering its ionized calcium concentration (calcium is required for the coagulation process). The extracorporeal blood ionized calcium level is lowered by infusing trisodium citrate (which complexes calcium) into the arterial line and by using a dialysis solution containing zero calcium. It would be very dangerous to return blood with a very low ionized calcium concentration to the patient. Thus the process is reversed by infusion of calcium chloride into the "venous" blood line distal to the dialyzer. About one-third of the infused

citrate is dialyzed away, and the remaining two-thirds is quickly metabolized by the patient.

An alternative and potentially simpler method of regional citrate anticoagulation, which will not be described here (see Von Brecht et al.) depends on citrate infusion only, and dispenses with the use of a zero calcium dialysis solution and with calcium reinfusion.

The advantages of regional citrate anticoagulation over heparin-free dialysis are (a) the blood flow rate does not have to be high and (b) clotting almost never occurs. The principal disadvantage is the requirement for two infusions (one of citrate and one of calcium), and the requirement for monitoring the blood calcium level. Because citrate metabolism generates bicarbonate, use of this method will result in a greater than usual increment in the plasma bicarbonate value. Hence regional citrate anticoagulation should be used with extreme caution in patients who are at risk for alkalemia.

1. **Method.** The technique described (provided courtesy of Dr. John C. Van Stone) has been validated only for dialysis using two blood access lines. The method given below has not been tested using single-blood-pathway dialysis, although others (von Brecht et al.) have described use of a citrate technique for single-blood-pathway dialysis as well.
   a. **Solutions.** Trisodium citrate for IV use is available from American Bentley, Inc., Irvine, Calif., and from the Haemonetics Corp., Braintree, Mass). The citrate is packaged in 30-ml vials containing 46.7% citrate (1.6 mol/liter). A stock solution (132 mmol/liter) is made by diluting three 30-ml vials into 1 liter of 6% D/W.

      Calcium chloride is obtained in 10% vials, 10 ml per vial. Five 10-ml vials (50 ml) are diluted with 100 ml of 0.9% saline (final concentration 3.33% or 467 mEq/liter).

      The citrate solution is administered into the arterial blood line (leading to the dialyzer) and the calcium solution into the venous blood line (leading from the dialyzer) using volumetric IV infusion pumps. Because the infusions may be opposed by pressures in the blood lines, IV infusion pumps that actually pump the solution, rather than those that deliver solution based on gravity drip, must be used.
   b. **Dialyzer and dialysis solution.** Any dialyzer can be used, but water permeability should be sufficient to easily allow removal of the extra 300 ml/hour of fluid that will be administered with the citrate and calcium infusions. The dialysis solution will usually be bicarbonate-buffered, given that the method is used primarily in unstable, intensive-care-bound patients. A zero calcium dialysis solution must be used.
   c. **Sample prescription.** The initial infusion rates of citrate and calcium described below are based on a blood flow rate of 200 ml/minute. If lower or higher blood flow rates are used, the infusion rates listed should be altered accordingly.
      (1) Obtain baseline clotting studies (WBPTT or ACT) and plasma total calcium level.
      (2) Initiate dialysis solution flow.
      (3) Initiate the citrate infusion into the arterial line at a starting rate of 270 ml/hour. Start the blood flow at the same time. Increase blood flow rapidly to 200 ml/minute. At a blood flow rate of 200 ml/minute, this citrate infusion rate will result in a citrate concentration of 3.6 mmol/liter in the blood entering the dialyzer.
      (4) Immediately start the calcium chloride infusion into the venous line at a rate of 30 ml/hour. At a blood flow rate of 200 ml/minute, this calcium infusion rate will result in an increase of about 1.2 mEq/liter in the blood leaving the dialyzer.
      (5) Check the patient's plasma total calcium level (sampling from the arterial blood line) 30 minutes after starting dialysis and then as needed. Adjust the calcium infusion rate to keep the plasma total calcium level within the normal range (the usual infusion rate of the calcium solution ranges from 24 to 42 ml/hour, average = 30–36 ml/hour).
      (6) Check the clotting time (WBPTT or ACT) periodically in the arterial line, downstream to the citrate infusion (reflects citrate effect). The WBPTT or ACT downstream to the citrate infusion should be prolonged by approximately 100%. If prolongation of the clotting time here is less than 100%, then one should increase the rate of citrate infusion (up to about 420 ml/hour). If the prolongation of the WBPTT or ACT here is greater than 100%, one may consider reducing the citrate infusion rate, although this is not always necessary. The patient WBPTT or ACT should not change during dialysis.
      (7) If the dialyzer goes into bypass mode due to some problem with the dialysis solution (the dialysis solution will then be shunted around the dialyzer directly to drain), the effect of the zero calcium dialysis solution will cease to occur. In this case, shut off the calcium infusion and reduce the citrate infusion rate by 50% until the flow of dialysis solution is restored. This method has *not* been tested to be suitable for extended operation in bypass mode, or for procedures in which dialysis solution is not used, such as isolated ultrafiltration.
      (8) At the end of dialysis, stop the citrate and calcium infusions simultaneously, and return the blood in the usual fashion.

CLINICAL DIALYSIS

Second Edition

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8 Anticoagulation in Patients on Hemodialysis

Richard D. Swartz

INTRODUCTION

The development of hemodialysis would be difficult to imagine without the availability of an easily administered systemic anticoagulant to prevent thrombosis in the extracorporeal tubing and dialyzer. Yet, heparin, the short-acting anticoagulant that has been the standard agent for hemodialysis, has presented a classical therapeutic dilemma, potentiating the risk of hemorrhage in patients who require hemodialysis treatment but are already at increased risk for bleeding. It is precisely because uremic patients requiring dialysis may suffer both hemorrhagic and thrombotic events that it is important to focus on the baseline coagulation status, on the use and complications of antithrombotics, and on the management of bleeding and clotting complications in this setting.

COAGULATION STATUS IN UREMIC PATIENTS: BLEEDING

Bleeding Tendency

Bleeding is a well-known and common complication in the uremic patient requiring dialysis, with qualitative platelet dysfunction being the most prominent and most consistently reported abnormality (Table 8–1).[1–9] Aggregation, adhesion, and release may all be disordered to some degree in uremia. In addition, endothelial abnormalities such as increased production of platelet-inhibiting prostaglandin derivatives may also contribute to both the specific platelet abnormality as well as to the abnormal bleeding time.[6,7] Dialysis appears to improve uremic platelet dysfunction and bleeding time, presumably the result of dialytic removal of circulating inhibitors of platelet function such as guanidinosuccinate and other "middle molecules."[8–10] Some reports even suggest that peritoneal dialysis may be more effective than hemodialysis in correcting platelet dysfunction, perhaps confirming better peritoneal clearance of platelet inhibiting metabolites having higher molecular weight.[11,12]

Other measures of coagulation, such as circulating levels of antithrombin III,[13–17] protein C,[18] factor XIII,[19] or other circulating factors,[17,20,21] are sometimes disordered in uremic patients. For example, abnormalities such as low antithrombin III[14,17] or protein C levels[18] may alter the response to antithrombotics such as heparin and be manifested as heparin resistance, but such abnormalities do not always result in measureable coagulation defects using the clinical tests generally available. In summary, although various reports demonstrate increases or decreases in circulating coagulation factors, no consistent or predictable pattern of abnormalities emerges among patients with renal failure.

Specific Sites at Risk for Bleeding

Serious bleeding complications have been described as a specific risk in general hospital patients whose medical and surgical complications include renal failure.[22] Bleeding from any site at risk may be more frequent and pronounced in patients with renal failure, but several unusual examples are particularly noteworthy. For example, the predilection to gastrointestinal bleeding from lesions such as gastritis, angiodysplasia, or rectal ulcers has been emphasized among dialysis patients.[23,24] Spontaneous uremic bleeding in the eye,[25] cranial cavity,[26,27] pericardium,[28,29] mediastinum,[30] and retroperitoneum,[31–33] has also been reported.

Often, it is even necessary to enhance coagulation, particularly platelet function, in order to stem bleeding in the uremic patient. Several therapies have been described in addition to dialysis itself, including the nonpressor vasopressin analogue DDAVP,[34] cryoprecipitate,[35] and high-dose conjugated estrogen,[22] which improve the bleeding time and may prevent further hemorrhage in some uremic patients. DDAVP and cryoprecipitate appear to have rapid onset within a few hours and short duration of 12 to 24 hours, whereas conjugated

TABLE 8–1. COAGULATION STATUS IN THE UREMIC PATIENT: BLEEDING

Bleeding tendency—abnormal bleeding time
Platelet dysfunction (multifactorial)
Possible vascular factors (humoral)
Specific bleeding sites at risk
General increased risk at common sites
Spontaneous bleeding
Gastritis, angiodysplasia, rectal ulcers
Intraocular
Intracranial
Pericardial
Mediastinal
Retroperitoneal

estrogens improve bleeding time within 12 hours and last several days. Any such therapy to enhance coagulation does not, however, obviate the need to treat the underlying bleeding lesion specifically and to achieve adequate dialysis therapy.

COAGULATION STATUS IN UREMIC PATIENTS: THROMBOSIS

Endogenous Thrombosis

Although impaired platelet function and a bleeding tendency characterize severe renal failure, thrombosis can also occur and is not unusual in several specific locations (Table 8–2). For example, clotting of the hemodialysis access, both the external cannula (shunt) as well as the endogenous arteriovenous fistula or synthetic vascular graft, is a common and troublesome problem.

TABLE 8–2. COAGULATION STATUS IN THE UREMIC PATIENT: THROMBOSIS

"Hypercoagulable" state (idiosyncratic)
Altered circulating coagulation factors
Antithrombin III
Protein C
Platelet related factors
Increased platelet activation
Underlying medical/surgical illness
Heparin induced
Thrombotic complications
Endogenous
Vascular hemodialysis access (shunt > subcutaneous graft > fistula)
Arterial, peripheral vascular
Deep veins with pulmonary embolism
Priapism
Extracorporeal, dialyzer and tubing
Physicochemical aberration in dialysate
Decreased blood flow rate
Increased hematocrit and viscosity
Platelet activation (membrane, drug)

Clotting of vascular access is sometimes treated acutely with thrombolytic agents[36] and prophylactically with antiplatelet agents[37–39] or even systemic anticoagulants such as coumadin.[40] It should be noted, however, that such therapy does not always prevent recurrent thrombosis in synthetic vascular grafts[41–43] and that complicating hemorrhage is a danger in this setting. Therefore, it is particularly important to evaluate carefully for outflow stenosis, for compressing extravascular hematoma or pseudoaneurysm, and for complicating access infection before initiating anticoagulant therapy in patients with hemodialysis access thrombosis.[41,44–47]

It has become clear that access longevity with respect to thrombosis, as well as other complications such as infection, is best achieved with the endogenous fistula and successively less so with the subcutaneous vascular graft and with external silastic cannula.[39,47] The recent tendency toward the preferential use of endogenous fistulas and grafts and the reduced reliance on external cannulas may decrease the need for prophylactic anticoagulants and obviate the subsequent risk of bleeding complications in many cases.

Spontaneous thrombosis in other locations, including peripheral arterial occlusion, deep venous thrombosis with pulmonary embolism, or priapism,[48,49] has also been reported in dialysis patients regardless of the bleeding tendency that ordinarily accompanies their illness. Some authors have even described a "hypercoagulable" state in certain patients,[18,20,50] thought to result from enhanced platelet activity the etiology of which has not been clearly defined.

Extracorporeal Thrombosis

Clotting in extracorporeal dialysis devices is also a common problem and has prompted extensive discussion of the need for anticoagulants during hemodialysis. Fibrin and platelet deposits in the interstices of plate dialyzers or in the capillaries of hollow-fiber dialyzers have been repeatedly described by both gross observation as well as by various qualitative and quantitative measures.[51–62] It has been estimated that extracorporeal heparinization to approximately 0.2 U/ml or more is sufficient to consistently prevent dialyzer thrombosis,[52, 63] and most studies report an incidence of substantial dialyzer clotting in 5% of cases or less with routine heparinization.[52,55,63–67]

Thrombosis in the extracorporeal dialyzers may be particularly prominent not only when preventive anticoagulation is reduced, but also when dialysate pH is low,[68] when extracorporeal blood flow is reduced,[55,66] or when whole blood hematocrit is increased.[59,62,69] Extracorporeal hematocrit can increase when a high ultrafiltration rate is employed to remove excess fluid during hemodialysis and can possibly predispose to dialyzer clotting. A therapy commonly required by uremic patients and administered during hemodialysis, blood transfusions can produce endogenous hemodynamic effects associated with increased hematocrit and viscosity[70] and may also predispose to dialyzer clotting. Both heparinization of the blood to be transfused during

hemodialysis as well as administration of the transfusion into the extracorporeal circuit downstream from the dialyzer may be helpful in reducing extracorporeal clotting under these circumstances. Increased hematocrit and viscosity also result from therapy with recombinant erythropoietin,[71] and these changes may predispose to clotting both in the endogenous vascular hemodialysis access as well as in the extracorporeal dialyzer when use of this agent in the general dialysis population becomes more common.

Since the initiation of dialyzer clotting may sometimes result primarily from platelet aggregation, and since heparin itself may sometimes initiate platelet activity,[72,73] it is not surprising that clotting is resistant to heparin alone and appears to improve with antiplatelet therapy in some cases.[74–77] Newer dialyzers, designed with a smaller priming volume, better laminar flow characteristics, and reduced intrinsic platelet activation by the membrane materials, may even require less heparin, although these requirements have not been established by systematic studies. More important, it is now recognized that, in some settings, hemodialysis can be successfully accomplished without using any systemic anticoagulant, particularly when thrombocytopenia or other coagulopathy is present (see below).

HEPARIN IN THE UREMIC PATIENT

Heparin Kinetics

The description of heparin activity in uremic patients generally focuses on the sensitivity to initial heparin loading and on the rate of elimination or half-life thereafter. Because the usual coagulation measurements are often normal in uremic patients, it is not surprising that heparin action is also relatively normal in these individuals. The rate of heparin elimination in uremic patients, as measured by a half-life ranging from 40 to 90 minutes,[64,78] tends to be relatively consistent in uremic patients and comparable with that in nonuremic individuals.[79] On the other hand, the sensitivity to heparin loading has been shown to vary by 100% or more between dialysis patients and from time to time in individual patients,[14,64,67,80–86] and doses required to achieve sufficient systemic anticoagulation in uremic patients may vary widely. This variability in sensitivity is also not unique to renal failure, and both uremic and nonuremic individuals manifest heparin sensitivity that varies with plasma volume (volume of distribution)[14,79] and to some degree with dose.[14,79] Some uremic patients may even be strikingly resistant to heparin, particularly in the presence of active thrombosis or underlying nephrotic or acute inflammatory disease,[30,80,84,86,87] as well as, theoretically, in the presence of excess ascorbic acid in dialysate.[88]

Side effects of heparin, such as pruritus, specific allergy, osteoporosis, or lipid abnormalities[89–92] do not appear to be specific or inordinate in uremic patients, nor have these side effects been associated with idiosyncratic variations in heparin sensitivity. Another striking complication of heparin administration, immunologic enhancement of platelet aggregation with thrombocytopenia and thrombosis,[94–97] is also not reported inordinately in the dialysis setting and does not account for most commonly observed variabilities in heparin sensitivity.

WORSENED BLEEDING ASSOCIATED WITH HEMODIALYSIS

Although it has been noted that dialysis may improve the bleeding tendency of uremia, there is, additionally, sufficient experience to suggest that hemodialysis with heparin may also increase both the frequency and severity of bleeding in patients who are at increased risk.[21,65–67]

The incidence of bleeding complications is known to increase in general hospital patients given heparin or antiplatelet agents,[67,98–100] and it is likely that the risk associated with heparin is exaggerated in patients with renal failure and its associated coagulopathy. For example, it appears that intracranial hemorrhage may be both more frequent and more severe in hemodialysis patients than in nonhemodialysis patients, perhaps a result of repeated intermittent heparinization.[27] Other studies suggest that the incidence and severity of any bleeding complications associated with heparinization during hemodialysis are directly related to acute bleeding risk as indicated by the presence of active or recent bleeding and of surgical or traumatic wounds within the previous 2 to 3 days.[66,67,101] The frequency of such bleeding may be as high as 50% in the first 24 hours after hemodialysis among the highest risk patients with preexisting active hemorrhage.[66,101] Furthermore, studies that compare hemodialysis using heparin with hemodialysis using alternative methods to prevent extracorporeal thrombosis suggest that even limited doses of heparin contribute to bleeding complications.[51,66,67,102]

DELIVERING AND MONITORING ANTICOAGULATION DURING HEMODIALYSIS

Systemic Heparinization

The standard method for anticoagulation during dialysis is systemic heparinization, often limiting the degree of systemic anticoagulant effect by monitoring one of several coagulation tests, including the partial thromboplastin time, thrombin clotting time, whole blood clotting time such as the Lee White clotting test, or some variation of the activated clotting time such as the ACT or Hemochron tests (Table 8–3).[80,102,104] The goal is, ordinarily, to control the degree of systemic anticoagulation by maintaining therapeutic heparinization at approximately two to three times the normal value for the chosen test. Comparative studies confirm the correspondence of

TABLE 8–3. DELIVERING AND MONITORING ANTICOAGULATION DURING HEMODIALYSIS

- Systemic heparinization
  - Standard loading and maintenance
  - Monitor with available test for heparin effect
    - Partial thromboplastin time
    - Thrombin clotting time
    - Whole blood clotting time (e.g., Lee-White)
    - Activated clotting time (or analogue)
  - Approximate goal 0.2 U/ml (two times normal value for tests)
  - Increased bleeding in patients at risk
- Regional heparinization
  - Heparin/protamine (cumbersome, questionable efficacy)
  - Citrate/calcium (cumbersome, effective)
  - Membrane treatment with protamine (unavailable)
  - Removal by heparinase (unavailable)
- Low-dose heparinization
  - Loading 5–10 U/KG; Maintenance 5–10 U/KG per hr or small bolus doses (250–500 U) as needed
  - Monitor with available test for heparin effect
  - Approximate goal below 0.10–0.15 U/ml (less than 1.5 times normal value for tests)
  - For CAVH: can use loading of 500 U or less; maintenance of 500 U/hr or less
- Alternative agents
  - Prostacyclin, prostacyclin analogues (no heparin)
  - Other platelet inhibitors (heparin-sparing agents)
  - Low-molecular-weight heparin (no controlled data)

these tests,[90,103–105] leaving the method of monitoring to the convenience and discretion of the practitioner.

Recognition of the increased risk of bleeding complications in patients requiring dialysis has, however, prompted clinicians to devise other methods for limiting the systemic effects of administered antithrombotic agents during hemodialysis.

Regional Anticoagulation

One method of controlling detectable systemic heparinization involves administration of heparin "regionally" into the blood entering the extracorporeal circuit, and neutralization of heparin by administration of protamine into the dialyzed blood as it returns to the patient.[92,93,107,108] By the precise control of dosage of these two agents, one can demonstrate the desired heparin effect in the dialyzer tubing, but no heparin effect in systemic blood. Over the years, this method has proven both cumbersome and difficult to control, requiring close monitoring with frequent coagulation tests of both the systemic and extracorporeal circuits.[66,102] Furthermore, studies describing this procedure fail to show controlled evidence for the efficacy of regional heparinization in preventing bleeding complications, with some reports even describing significant bleeding complications regardless of well-monitored regional heparinization.[51,88,109] More important, in a controlled comparison of regional and tightly monitored low-dose heparinization, bleeding complications were at least as frequent using regional heparinization.[66] This persistent incidence of bleeding in the face of adequate regionalization is probably the consequence of the requirement for high total heparin doses,[60] of dissociation of the heparin–protamine complex,[109–111] and of the effects of protamine itself.[112,113] The difficulty of performing regional heparinization and the absence of proven efficacy have severely limited more general application of this method for control of systemic anticoagulation during hemodialysis.

Another method for regional anticoagulation involves administration of citrate to chelate calcium in the extracorporeal circuit and neutralization with calcium itself in blood returning to the patient. This method takes advantage of both rapid citrate metabolism as well as citrate dialyzability to limit systemic side effects, and has proven effective in limiting the incidence of hemodialysis-associated bleeding in controlled comparisons with low-dose heparin.[101,114] Dialyzer clotting observed using this method appears to be quantitatively equal to that using low-dose heparin,[101] and may be due in part to possible platelet aggregation in the presence of citrate.[115] Regional citrate hemodialysis is reliable in experienced hands; however, the complexity of monitoring, the potential danger of hypocalcemia and the availability of simpler methods for minimizing systemic anticoagulation, appear to have limited the general application of this method.

A promising variation of the regional anticoagulation method is the use of protamine permanently bonded to membranes to remove heparin from the blood. This method has been demonstrated in vitro,[116] but has not yet been applied to hemodialysis or related extracorporeal procedures in the clinical setting. Development of systems applicable to hemodialysis might better prevent unwanted systemic anticoagulation while successfully preventing extracorporeal thrombosis.

Another method for regional neutralization of heparin is enzymatic degradation using a filter containing heparinase.[117,118] Placing such a device in the extracorporeal circuit at the site of reinfusion would eliminate active heparin from blood returning to the patient. Again, although such devices have been described in laboratory models,[117,118] no clinical testing has been reported. In addition, there is some concern that degradation of heparin leads to circulation of heparinoids and heparin fragments that will be active anticoagulants or will lead to toxic or allergic reactions.[119]

Low-Dose Heparinization

A straightforward method for limiting systemic anticoagulation during hemodialysis is simply to limit total heparin dose by reducing administration rate and by monitoring with one of the standard tests to keep the heparin effect to below 1.5 times the normal nonheparinized value for the chosen test. Using such "tight" protocols, hemodialysis can be accomplished with total heparin doses below 1000 U/hr without serious extracorporeal clotting complications.[54,93,99,107,63,102] Often, even lower heparin doses, well below the range of 10 U/kg to

load and 10 U/kg per hr, will suffice, and empiric dosing in this range is common.

Strict limitation of heparin during hemodialysis is not accepted uniformly, and some authors report frequent clotting in the dialyzer unless heparin doses of more than 1000 to 1500 U/hr are used.[60,106,120] Therefore, in an effort to individualize dosing and allow tighter control whenever possible in high-risk circumstances, it is sometimes suggested that heparin sensitivity be tested prospectively and heparin effect be monitored closely during therapy.[55,64,67,83,103,106,120] Several authors have described testing individual sensitivity in vitro using the thrombin clotting time,[60,67,105] or in vivo using modest single heparin doses prior to dialysis.[55,64] Such sensitivity testing may, however, prove cumbersome to use routinely, may not always be feasible at initiation of acute hemodialysis, and may even prove dangerous in itself if performed in vivo in patients at risk for bleeding. In high-risk circumstances, it may be sufficient first to choose a low initial loading dose of heparin, for example, 5 to 10 U/kg, and second to maintain the value of a readily available clotting test, such as the whole blood clotting time or the ACT, below 1.5 times normal using either low-dose infusion of 5 U/kg per hr or intermittent, small bolus doses of 250 to 500 units.

Continuous arteriovenous hemofiltration (CAVH) also requires ongoing low-dose anticoagulation and is applied in critically ill patients who often have increased risk of bleeding, presenting the practitioner with the same dilemma as hemodialysis. Strict monitoring of heparin[121] and regional heparinization[122] have both been used successfully during CAVH. It also appears, however, that empiric low-dose therapy with 500 U/hr or less may suffice to maintain filter patency during CAVH.[121,123] Further experience with this new renal substitution method will help to better define the heparin requirements and the applicability of other methods for preventing extracorporeal clotting.

Hemodialysis Without Anticoagulation

Regardless of the general feeling that some heparin is necessary to prevent extracorporeal clotting, and that limited heparin dosing is useful in patients at increased risk for bleeding, some investigators have now systematically described several methods for performing hemodialysis without any anticoagulation.[50,56,59,61,62,124] The risk of extracorporeal clotting may be somewhat higher without anticoagulation, as frequent as 20% on average.[59,61,62] It appears, however, that hemodialysis can be successfully performed without anticoagulation in an as yet undetermined number of acute and chronic cases.

Several important factors have been introduced that may facilitate hemodialysis without anticoagulation. First, newer dialyzers have smaller blood volume and higher blood velocity at standard blood flow rates, reducing the tendency to clotting. Second, newer membrane materials may be more biocompatible and reduce platelet activation and early clotting.[125–129] Third, some authors have described intermittent high-volume saline flushing to clear the dialyzer during treatment.[56,59] This saline flushing introduces extra fluid that must then be removed by higher transmembrane pressure, perhaps both limiting the usefulness of this method in some fluid overloaded patients as well as necessitating added ultrafiltration and hemoconcentration that may actually promote dialyzer clotting.

It is clear that peritoneal dialysis can also be performed in order to avoid anticoagulation entirely in patients with increased risk of bleeding. Nonetheless, severe abdominal pathology may obviate this procedure in some cases and necessitate hemodialysis or a related extracorporeal therapy, in which case strict attention to limiting systemic anticoagulation will be essential.

Alternative Agents

It is difficult to imagine an alternative to heparin that is as readily available, as inexpensive, and as easily used and monitored. Yet the danger of heparin in some circumstances is clear, and several alternatives have been described. The best known of these alternative agents is PGI2 (prostacyclin; epoprostenol), the inhibitor of platelet aggregation produced naturally by endothelial cells. This agent has a very short half-life of 30 seconds or less in vivo,[130,131] and inhibits platelet aggregation dramatically for 5 to 30 minutes and to a much lesser degree thereafter.[130–135] The agent is infused into the blood as it enters the extracorporeal circuit at doses of 4 ng/kg per min or less, doses sufficient to effectively inhibit platelet activity. Although the major shortcoming of this agent is its concomitant vasodilatory activity, which sometimes causes flushing, headache, nausea, and varying degrees of dose-related hypotension, hemodialysis can be successfully performed with a minimum of serious side effects.[132,135–139] More important, randomized controlled trials among patients with increased bleeding risk show PGI2 to be associated with significantly less dialysis-associated bleeding.[140] A more stable prostacyclin analogue has been used successfully in animals undergoing hemodialysis without other anticoagulants, although the agent still has similar vasodilatory side effects to prostacyclin itself.[141] The theoretical advantages and preliminary success with this type of agent warrant further development.

Other platelet inhibitors such as ticlopidine[142] and sulfinpyrazone[60,70,72] have been used in conjunction with heparin as dose-sparing agents. These agents have not however, been used as the sole antithrombotic in hemodialysis. In similar fashion, nonsteroidal agents such as aspirin have also been used as auxiliary agents to reduce the frequency of intradialytic thrombosis, particularly in patients with excessive clotting.[69]

Low-molecular-weight heparin has also been described as an alternative to heparin itself, purportedly having a more predictable anticoagulant effect because of slower elimination in dialysis patients who lack renal function.[143–145] Furthermore, these compounds may be more effective in preventing dialyzer clotting because they induce less intrinsic platelet aggregation than does

standard heparin.[145] Use of such agents in hemodialysis has proven feasible, with only minor increases in dialyzer clotting under conditions of chronic stable hemodialysis. Other advantages such as increased controllability and reduced bleeding complications are, however, yet to be clearly demonstrated.

Extracorporeal Intrinsic Antithrombotics

Another mechanism for preventing extracorporeal thrombosis that avoids systemic anticoagulation involves bonding of heparin or related compounds to the material used in manufacture of tubing or dialysis membrane.[66,147–149] Nevertheless, this attractive concept has received only sparse attention in the clinical literature, and a reliable system has not yet been developed for general clinical application. Furthermore, the problem of platelet activation may still need to be addressed before a successful method of this type is operational.

SUMMARY

The Bleeding Patient

Evidence supports the notion that heparin administration during hemodialysis exacerbates bleeding in uremic patients when the risk for bleeding is increased (Fig. 8–1). In approaching such a situation, the first con-

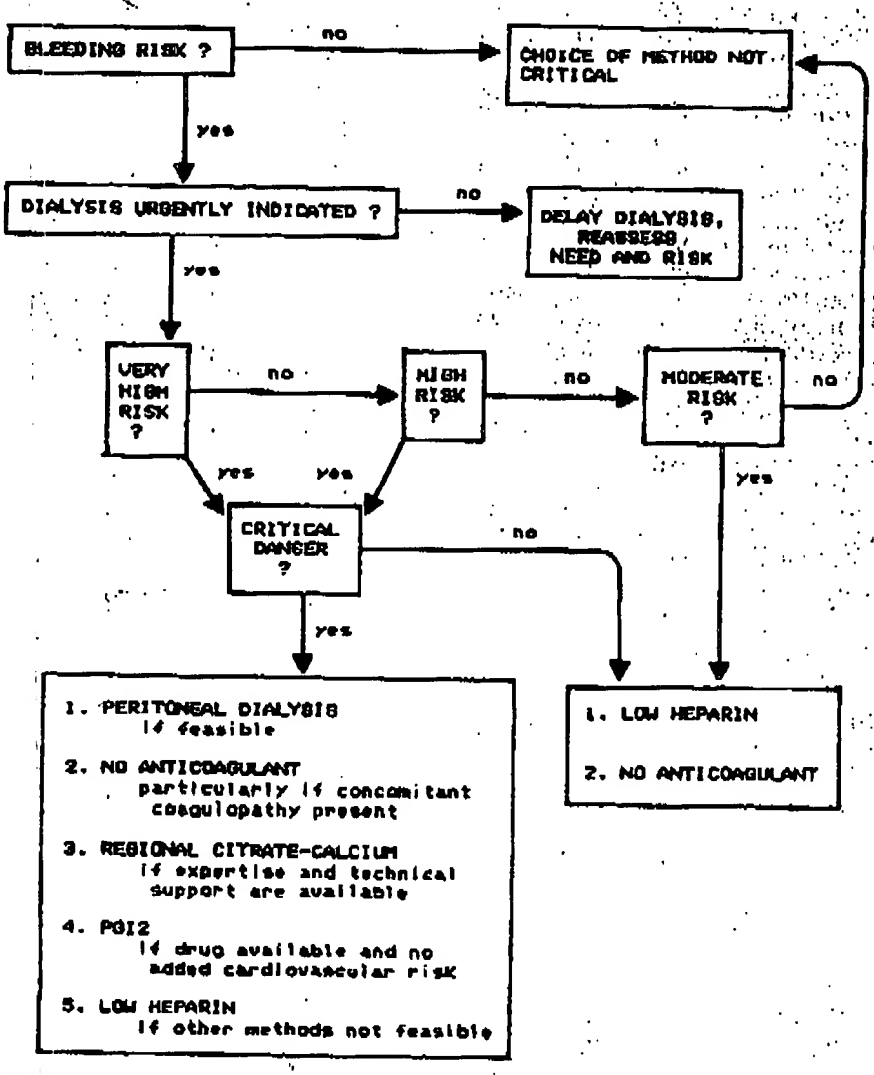

Figure 8–1. Decision analysis for anticoagulation method in the patient with increased bleeding risk. Degree of risk defined as:[66,67] VERY HIGH—active bleeding at the time of dialysis; HIGH—active bleeding or surgical/traumatic wound within 3 days; MODERATE—active bleeding or surgical/traumatic wound within 3–7 days. "CRITICAL DANGER" defined in text. Numerical order of choice indicates order of preference.

sideration is the necessity of the dialysis itself, as delay for 48 hours or more may reduce the risk of bleeding complications associated with anticoagulation during hemodialysis.[66,67] When dialysis cannot be delayed, the decision regarding the method for reducing the incidence and severity of unwanted bleeding is influenced by the precise nature of the risk—more important when the bleeding is active and involves vital function, such as occurs in the cranial cavity or pericardium, and less important when bleeding is no longer active and when blood loss can be replaced without further acute danger, such as occurs in the gastrointestinal tract or external wound. The rate and source of bleeding may also influence the assessment of "critical danger," as occurs with brisk arterial bleeding. When the risk is higher and the danger more critical, the chosen modality should avoid anticoagulation if possible (peritoneal dialysis or hemodialysis without anticoagulant), with other possibilities when the preferred choices are not feasible or have failed. When the risk is lower and/or the danger less critical, the choice of modality is less problematic, and even tightly controlled low-dose heparin, which is relatively simple, may suffice.

Mechanical methods to remove heparin such as membrane-bound protamine or heparinase have not been developed sufficiently for general clinical use. In some patients with severe bleeding worsened or unimproved by dialysis, additional therapy may be necessary with agents that improve the bleeding time by modulating platelet function and/or vascular factors. Such agents include DDAVP, cryoprecipitate, and high-dose conjugated estrogen, but thrombosis in remote locations such as the hemodialysis access is a possible risk of such therapy.

The Clotting Patient

Regardless of the bleeding tendency that characterizes patients who require dialysis, problematic thrombosis is not uncommon. Clotting in the extracorporeal system during hemodialysis can be potentiated by low extracorporeal blood flow rate, higher whole blood hematocrit, and enhanced platelet aggregation. Extracorporeal clotting may be prevented by anticoagulant administration, including adequate heparin therapy or antiplatelet agents of acute type, such as prostacyclin, or chronic type, such as sulfinpyrazone, and possibly by the use of more biocompatible dialyzers that are less liable to stimulate platelet aggregation. Clotting in the endogenous circulation is particularly problematic in the hemodialysis vascular access and is potentiated by anatomic abnormalities in the vessels involved. Such clotting is occasionally treated with systemic anticoagulant or antiplatelet therapy, although this therapy poses the risk of additional interdialytic bleeding for the dialysis patient.

Conclusion

It is clear that the necessity for acute or ongoing chronic hemodialysis in some uremic patients presents a difficult dilemma involving the risk of exacerbating an underlying hemorrhagic tendency and the simultaneous need to prevent extracorporeal or endogenous clotting. Resolving this dilemma involves both thoughtful planning of dialysis and drug therapy as well as careful monitoring for bleeding and thrombosis, a significant challenge for the conscientious practitioner.

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Hemodialysis Without Anticoagulation

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● Heparin is usually employed as an anticoagulant during routine hemodialysis. In patients at high risk of bleeding, however, use of heparin significantly increases their morbidity and, presumably, mortality. Over 1 year, we performed 156 hemodialysis procedures successfully without heparin in the transplant dialysis unit. Twenty-eight patients were included in the study: 23 patients had received renal transplants and five patients were in the perioperative period for surgery not relating to transplantation (bilateral nephrectomy, cholecystectomy, full-mouth dental extraction, and parathyroidectomy). Only one of these patients had a coagulopathy. No dialysis procedure produced or aggravated bleeding. Conversely, a coagulopathy was not induced or worsened by dialysis without heparin. A significant complication, defined as complete clotting of the artificial kidney with or without clotting in the lines, occurred in eight dialyses (5.13% of the total) and resulted in an average blood loss of 150 ml. Partial clotting of the dialyzer did not interrupt the procedure and occurred nine times (5.8% of the total). These results compare favorably with previously documented complications from low-dose and regional heparin.

INDEX WORDS: Hemodialysis; anticoagulation; heparin; transplantation.

ROUTINE HEMODIALYSIS is generally performed using heparin as an anticoagulation agent to avoid clotting of the blood while it circulates in the dialysis apparatus.[1,2] However, the systemic anticoagulation that results from heparinization can produce dramatic hemorrhagic complications in those patients who are at high risk of bleeding or who are actively bleeding but are in need of hemodialysis. Consequently, various "best" solutions for this clinical dilemma have been proposed, including regional heparinization,[3,4] low-dose heparin,[5,6] and more recently, prostacyclin.[7,8] These techniques are not without complications. We have previously suggested that it is sometimes possible to perform a complete hemodialysis without use of any anticoagulation in patients at risk of severe bleeding.[9] We now present a retrospective review of 156 complete hemodialysis procedures performed without heparin or other anticoagulants over a 1-year time period.

MATERIALS AND METHODS

During the period from August 1982 to August 1983, 130 patients who received either cadaveric or living-related donor transplants were dialyzed in the transplant dialysis unit. Of these patients, 23 (17.7%) were hemodialyzed at least once without heparin. In addition, five patients were dialyzed without heparin in the transplant dialysis unit because of preoperative or postoperative status not relating to transplantation and they are included. A total of 156 dialyses on these patients were performed without heparin. No patient received aspirin or other nonsteroidal anti-inflammatory agents in the period when hemodialysis was performed.

Indications for hemodialysis without heparin included (1) recent history of active bleeding, (2) pericarditis, and/or (3) preoperative (immediate) or postoperative status (status following transplant implantation, transplant nephrectomy, exploratory celiotomy, bronchoscopy, percutaneous renal biopsy, or dental extraction).

Every dialysis was carried out with a Drake-Willock Proportioning Unit and standard Cordis-Dow tubing (both from Cordis Dow Corp, Miami, Fla.). The lines and the kidney were rinsed initially with 1 L 0.9% sodium chloride with 3,000 U of heparin added. In every instance, this priming volume was displaced such that little, if any, heparin was given to the patient. The type of artificial kidney used depended upon the goals of the dialysis: volume removal, clearance, or both. Only Cordis-Dow or Travenol (Travenol Corp, Deerfield, Ill.) hollow-fiber kidneys were utilized and included CD 135, CD 1.8, CD 9500,

The hemodialysis procedure varied from the standard technique in the following respects: (1) Blood flows were kept between 280 and 300 mL/min except when contraindicated (eg, poor cardiovascular status or excessive hypotension during dialysis) or when it was impossible secondary to a poorly functioning graft or other physical limitations. (2) To examine the extracorporeal circuit, about 100 mL of saline was infused via the arterial limb every 20 to 30 minutes to visualize the kidney for evidence of clotting, and the transmembrane pressure was adjusted accordingly to prevent unnecessary volume expansion in the patient. (3) Lee-White clotting times were performed about every 30 minutes but no heparin was given. Duration of dialysis ranged between 2 and 4.5 hours with a mean duration of 3.74 hours. Predialysis platelet counts were available on 81 occasions and were examined, while prothrombin and/or partial thromboplastin times were obtained before 70 dialysis procedures. In 94 dialyses, predialysis and postdialysis urea nitro-

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gen and creatinine were performed to assess dialysis efficiency. Predialysis and postdialysis weight and hematocrit were available in 143 and 97 hemodialysis procedures, respectively. Sodium and potassium measurements were obtained before and after 79 and 82 dialyses, respectively.

A significant complication was defined as complete clotting of an artificial dialyzer and/or clotting of the arterial or venous lines. Blood loss was estimated by noting which portion(s) of the extracorporeal circuit had clotted. Standard volume for the lines is 172 mL, while the priming volume of the artificial kidney is between 65 and 101 mL, depending upon the type used. A completely clotted extracorporeal system would result in a maximal blood loss of 273 mL. Partial clotting of the artificial kidney or lines was determined by visual examination. This method, of course, will not detect low-grade clotting within the kidney; but, for the purpose of detecting significant blood loss, [illegible]

real circuit were examined when available. Arterial and venous pressures were monitored in 89 and 152 hemodialysis procedures, respectively.

Statistical analysis was performed by means of the paired Student's *t* test. A *P* value of less than 0.01 was considered significant. Results are expressed as mean ± SD.

RESULTS

Twenty-eight patients were dialyzed a total of 156 times (mean of 5.6 hemodialyses per patient) without need of heparin (Table 1). Thirty-nine percent were female and 61% were male. The age range was 19 to 56 years with a mean of 34.2 years. Most of the patients (86.9%) had received cadaveric renal transplants. Seventy-two (46.2%) [illegible] were performed without anticoagulation because of preoperative or postop-

Table 1. Compilation of Data on the 28 Patients in the Study

Patient No.	Age (yr)	Sex	Underlying Renal Disease	Type of Transplant	Reasons for Dialysis Without Heparin	No. of Dialyses	Significant Complications	Partial Clotting of Dialyzer
1	32	F	Diabetic nephropathy	Cadaver	Pericarditis	6	None	None
2	25	F	Lupus nephritis	LRD*	Intraperitoneal bleed; transplant surgery†	16	None	None
3	19	M	Reflux nephropathy	None	Other surgery‡	2	None	None
4	34	F	Polycystic kidneys	None	Other surgery	3	None	None
5	20	F	Reflux nephropathy	None	Other surgery	6	None	None
6	39	F	Reflux nephropathy	Cadaver	GI bleed; other surgery	17	None	None
7	33	M	Chronic glomerulonephritis	Cadaver	GI bleed; other surgery	8	None	None
8	44	M	Malignant hypertension	Cadaver	Transplant surgery	1	None	None
9	26	F	Obstruction	LRD	Transplant surgery	4	None	None
10	47	M	Polycystic kidneys	Cadaver	Transplant surgery	7	None	None
11	42	M	Unknown	Cadaver	GI bleed; other surgery	2	1	None
12	39	M	Polycystic kidneys	Cadaver	Transplant surgery	1	None	None
13	26	F	Fabry's disease	LRD	Uremia; possible GI bleed	2	None	None
14	39	M	Membranous glomerulonephritis	Cadaver	Transplant surgery	1	None	None
15	32	M	Chronic glomerulonephritis	Cadaver	Transplant surgery	1	None	None
16	30	M	Unknown	Cadaver	Other surgery	3	1	1
17	31	M	Malignant hypertension	Cadaver	GI bleed; transplant surgery	2	1	None
18	24	M	Reflux nephropathy	Cadaver	Transplant surgery	2	None	None
19	46	M	Unknown	Cadaver	Transplant surgery; other surgery	3	None	None
20	56	F	Lupus nephritis	None	Other surgery	2	None	None
21	56	F	Obstruction	Cadaver	Transplant surgery	2	None	None
22	19	M	Unknown	Cadaver	Transplant surgery	5	None	None
23	36	M	Hereditary nephritis	Cadaver	Transplant surgery; GI bleed; other surgery; hemoptysis	49	5	6
24	33	F	Reflux nephropathy	Cadaver	Transplant surgery; hematuria	3	None	None
25	49	F	Unknown	None	Other surgery	1	None	None
26	19	M	Reflux nephropathy	Cadaver	Transplant surgery	1	None	None
27	39	M	Unknown	Cadaver	Wound hemorrhage	3	None	None
28	23	M	Reflux nephropathy; focal glomerulosclerosis	None	Other surgery	9	None	None

*LRD = living-related donor.
†Transplant surgery includes graft implantation or nephrectomy.
‡Other surgery includes bronchoscopy, percutaneous renal biopsy, full-mouth dental extraction, and exploratory celiotomy.

erative status, while 78 (50%) were done because of active or recent hemorrhage (gastrointestinal, wound, urinary tract, or pulmonary). The remaining six (3.8%) were performed in the setting of acute pericarditis.

The average platelet count was 158,100/μL and the average clotting time was 13.7 minutes. In only one patient was a coagulopathy present, and she was dialyzed a total of 16 times. No appearance or notable increase in hemorrhage was found, and hemodialysis without heparin did not appear to exacerbate or induce a coagulopathy in any patient. Significant complications occurred in eight dialyses (5.13% of total) with an average estimated blood loss of 150 mL and maximal loss of about 250 mL. No hemodynamic compromise from this blood loss was noted, and besides the blood loss, the only other significant problem was the time delay required to change the kidney and lines. Partial clotting of the artificial kidney did not interrupt dialysis and occurred nine times (5.8%). Predialysis and postdialysis Hct were 26.1 ± 5.7% and 24.3 ± 6.2%, respectively, and were not significantly different (P = NS). Arterial pressures and venous pressures in the extracorporeal circuit increased by 6.1 ± 20.0 mm Hg ($P < 0.005$) and 17.4 ± 26.4 mm Hg ($P < 0.001$), respectively.

To assess dialysis efficiency, predialysis and postdialysis urea nitrogen, creatinine, body weight, sodium, and potassium were examined (Table 2). Clearances were adequate in each instance with near normalization of the urea, creatinine, sodium, potassium, and water balance occurring in all hemodialysis procedures, except for [illegible] in which the patient was [illegible] tensive most of the time. Except in the patient with a coagulopathy, prothrombin times and partial thromboplastin times were not prolonged.

DISCUSSION

Fear of blood loss from clotting in the extracorporeal system is the major reason for heparinization during dialysis. However, the problems of replacing a clotted dialyzer with its attendant loss of blood seem small compared with the risk of provoking uncontrollable hemorrhage in high-risk patients. These patients include those who are in a perioperative period, have recently hemorrhaged, or are actively bleeding. Others have also elected to try a no anticoagulation approach with success.[10-13] This retrospective report suggests that the risks of no heparin were indeed acceptable with significant blood loss (maximum 250 mL and average loss of 150 mL) occurring in only 5.1% of the dialyses performed. Moreover, the technique was not used in only the most exceptional cases, but was successfully performed for nearly 18% of the transplant patients who required back-up hemodialysis during the period of study. The dialysis without heparin was effective in clearing urea, creatinine, water, and potassium (Table 2), required only slightly more technical supervision, and allowed avoidance of use of anticoagulation, which could have resulted in clinical deterioration from hemorrhage.

The other techniques to limit anticoagulation are not without their risks and side effects. Regional heparinization was an early solution to the problem.[3,4] The technique proved cumbersome, requiring close monitoring of the clotting time along with two constant infusion pumps to administer the heparin and protamine. In addition, clotting in the extracorporeal circuit and rebound bleeding several hours after dialysis were not infrequent.[4] In 1979 [illegible] with the use of regional heparinization and low-dose heparin.[5] They reported a 19% incidence of bleeding complications with regional hepariniza-

Table 2. Comparison of Predialysis and Postdialysis Laboratory Parameters and Body Weight

Parameter	Predialysis	Postdialysis	P Value	No. of Dialyses
Sodium (mEq/L)	135.0 ± 5.5	137.3 ± 3.2	< 0.001	79
Potassium (mEq/L)	4.5 ± 0.8	3.3 ± 0.6	< 0.001	82
Bicarbonate (mmol/L)	22.4 ± 5.2	22.2 ± 3.9	NS	79
Hematocrit (%)	26.1 ± 5.7	24.3 ± 6.2	NS	97
BUN (mg/dL)	105.3 ± 34.2	44.4 ± 17.2	< 0.001	94
Creatinine (mg/dL)	9.15 ± 4.2	4.67 ± 2.3	< 0.001	94
Body weight (kg)	58.0 ± 15.1	56.1 ± 14.8	< 0.001	143

NS = not significant.

tion, compared with a 10% incidence with low-dose heparin. However, in very high-risk patients (those patients who were actively bleeding at the time of dialysis), hemorrhage worsened in 47% when regional heparinization was used and in 38% when low-dose heparin was employed. For high-risk patients, defined as those patients who had an episode of active bleeding within three days or who were dialyzed less than three days after an operation, hemorrhage occurred in 23% during regional heparinization and in 11% during low-dose heparinization. Using either of these techniques, no artificial kidney was lost because of clotting but partial clotting occurred in 3% to 5%. These results were comparable to those [illegible] in 1981.[9] By contrast, we noted no increase in hemorrhage attributable to hemodialysis in our patients. Significant clotting in the extracorporeal circuit occurred in 5.1% and partial clotting of the dialyzer occurred in 5.8%. Thus, it appears the risk of blood loss from clotting of the dialyzer is less than the risk of hemorrhage even when low-dose heparin is used in these high-risk patients. Prostacyclin has recently been used as an anticoagulant for high-risk dialyses.[8] The complication rate was significant, with severe hypotension occurring in 20%, chest pain in 20%, and other side effects (nausea, headache, flushing, abdominal pain) noted in many of the patients. We believe dialysis without heparin to be as least as efficacious as dialysis with prostacyclin, and we suggest that it is better than other methods used to control heparin dosage.

The reason hemodialysis without heparin can be successfully performed with minimal morbidity is uncertain. As mentioned, except in one patient who had a disseminated intravascular coagulopathy, prothrombin and/or partial thromboplastin times were normal. Also, the average platelet count was greater than 150,000/μL. One factor that we believe helps to prevent significant clotting in the extracororeal circuit is the high blood flow rate in the range of 280 to 300 mL/min. Every effort was made to maintain these flow rates, but in several cases, dialysis without heparin could be done with flow rates at or below 200 mL/min. Finally, since several types of both Cordis Dow and Travenol hollow-fiber kidneys were used successfully in this study, the type of artificial kidney did not appear to be a significant factor.

It is clear that hemodialysis without heparin should not be used routinely in stable patients. We believe that hemodialysis without heparin is indicated in those patients who (1) are immediately preoperative or within three to five days postoperative; (2) have recently hemorrhaged or are actively bleeding; or (3) have another strong contraindication to heparin such as pericarditis. From our data, we conclude that the risk of performing dialysis without anticoagulation is much less than the benefits in the high-risk patients.

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